REMARKS

Claims 1, 3, 4, 7-9, 11, and 47-62 remain pending in the subject application, of which claims 47-62 are withdrawn.

In the Final Action dated September 8, 2010, claims 1, 3, 4, 7-9, and 11 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over WO 01/054701 A1 ("Ho et al.") in view of WO 00/28003 A1 ("Kent et al."). Specifically, the Examiner asserted that Ho et al. discloses a method of permitting cessation of antiviral therapy on HIV-infected subjects, without virus rebound or with at least a delayed virus rebound or a decreased post-rebound viral load, by administering an attenuated recombinant poxvirus that includes nucleic acids encoding one or more HIV-specific immunogens. While the Examiner admitted that Ho et al. does not disclose co-expressing IFN-γ with an HIV antigen in the poxvirus vector, the Examiner relied upon Kent et al. which allegedly discloses an immunogenic construct comprising an avipox virus vector that encodes HIV-1 Gag and/or Pol and interferon-gamma (IFN-γ), and that was effective in inducing, enhancing or otherwise stimulating an immune response to HIV Gag and/or Pol.

Applicants traversed the Final Rejection in a §1.116 Response filed on November 8, 2010. Applicants submitted therein that the method of Ho et al. was not effective in permitting cessation of antiviral therapy on HIV-infected subjects, without virus rebound or with a delayed virus rebound or a decreased post-rebound viral load. In particular, Applicants pointed out that in Ho et al., when four patients chose to discontinue antiretroviral therapy after treatment with the protocol summarized above, only two of the four patients exhibited a "delayed rebound" in plasma viremia. Applicants also provided a report by Markowitz et al., which Applicants believe to cast doubt on the statistic significance of the observations made by Ho et al. Furthermore, Applicants asserted that those skilled in the art would not have been motivated to further enhance

the immune response against HIV by combining the method of Ho et al. with the teaching of Kent et al., in light of the lack of a correlation between immunogenicity and viral control during treatment interruption, as reflected by failed attempts in the art. In addition, Applicants submitted that those skilled in the art would not have had a reasonable expectation of success in arriving at the claimed invention, and the results achieved by the claimed invention were entirely unexpected.

The Examiner issued an Advisory Action on November 19, 2010, in which the Examiner asserted that Ho et al. is not required to demonstrate "100% success with all vaccination trials." The Examiner also stated that Markowitz et al. does not cite or mention Ho et al. nor does it cast doubt on the observations made by Ho et al. According to the Examiner, "[i]t is possible that Markowitz et al. performed a different experiment from Ho et al." In response to Applicants' remarks regarding a lack of motivation to combine Ho et al. and Kent et al., the Examiner has essentially asserted that even without the disclosure of Kent et al., those skilled in the art would know that IFN-γ can be combined with the vaccine taught by Ho et al.; and that failures in the art do not negate the results of Ho et al.

Applicants respectfully traverse the Examiner's assertions in the Final Official Action and the Advisory Action dated November 19, 2010.

Ho et al. Does Not Provide Adequate Teaching and Markowitz et al. Casts Doubt on the Results of Ho et al.

Applicants respectfully submit that it is apparent that Ho et al. and Markowitz et al. disclose data from the same clinical study. Specifically, Applicants note that both Ho et al. and Markowitz et al.:

i) list each of David Ho and Martin Markowitz as "Inventors" and authors, respectively;

ii) indicate that the studies disclosed were conducted in the Aaron Diamond AIDS Research Center of Rockefeller University;

iii) disclose seemingly identical vaccination agents, namely "ALVAC vCP1452" and "recombinant gp160";

iv) disclose studies of subjects accorded the identifiers "313-2", "1306", "1308", "1309", "1310", and "3002"; and

v) disclose strikingly similar data for the subjects accorded the identifiers "1306","1308", "1309", "1310", and "3002".

Applicants submit that Ho et al. is at best a selective disclosure of these data while Markowitz et al. is believed to be a more complete account of the clinical study. Applicants note that Ho et al. discloses detailed data for four subjects, namely "1306", "1308", "1309", and "1310" (page 32, line 27, to page 33, line 19), whereas Markowitz et al. discloses detailed data for eleven subjects, including "1306", "1308", "1309", and "1310" (page 637, Table 2, Group 1), as well as details for a further five subjects (page 637, Table 2, Group 2).

Further, Markowitz et al. discloses numerous failed attempts to prevent viral rebound after cessation of retroviral drug therapy which Ho et al. does not disclose. Specifically, Applicants note Ho et al.'s disclosure that when four subjects chose to discontinue antiretroviral therapy after treatment with the disclosed protocol, only two of the four subjects exhibited a "delayed rebound" in plasma viremia (subjects "1309"[1] and "1306"; page 33, lines 11-17). In contrast, Markowitz et al. discloses that when antiretroviral therapy of eleven patients was discontinued after treatment with the disclosed protocol, only two of the eleven patients

[1] Applicants note that Ho et al. disclose that "[p]ost-therapy discontinuation subjects 1310 and 1306 rebounded after 68 and 85 days respectively" (page 33, lines 11-12; emphasis added). Applicants respectfully submit that the identifier "1310" is a typographical error for "1309" when considered with the entire disclosure of Ho et al.

exhibited a "delayed rebound" in plasma viremia (page 637, Table 2, Group 1). Applicants further note that the two subjects that exhibited a "delayed rebound" in plasma viremia disclosed by Markowitz et al. were subjects "1306" and "1309", i.e., the same subjects disclosed by Ho et al.

Applicants further submit that Markowitz et al. essentially acknowledges that the two incidences of "delayed rebound" in plasma viremia disclosed may be chance. It is generally understood that if a statistically significant effect is observed then the results of a clinical study are said to be "positive"; however, if a statistically non-significant effect is obtained then the results are generally said to be non-significant, i.e. the effects obtained could result from chance alone. If statistically non-significant effects are observed, a disclosure may suggest that the effects may in fact be "real" but indicate that further work is required to establish whether or not this is the case. Markowitz et al. discloses that "[w]hen comparing the characteristics of virus rebound in vaccinated subjects versus subjects treated with HAART alone, we could not identify significant differences in the time to virus rebound ($P = .22$) . . ." (sentence spanning pages 638-39). Therefore, Markowitz et al. acknowledges that the incidences of "delayed rebound" in plasma viremia observed with subjects "1306" and "1309" are not significant. Furthermore, Markowitz et al. acknowledges the limitations of the clinical study disclosed, and indicates that "[w]e believe that further intensive study of these subjects, particularly those who appear to suppress viremia in the absence of detectable immune responses, is clearly indicated and is in progress" (page 642, second full paragraph, last sentence; emphasis added). Based on these discussions in Markowitz et al., Applicants respectfully submit that Markowitz et al. is suggesting that the only two incidences of "delayed rebound" in plasma viremia may be the result of chance.

Because Ho et al. and Markowitz et al. disclose data from the same clinical study but Markowitz et al. is a more complete account of the clinical study, because Markowitz et al. discloses numerous failed attempts to prevent viral rebound after cessation of retroviral drug therapy that Ho et al. does not disclose, and because Markowitz et al. apparently acknowledges that the two "successful" attempts to prevent viral rebound after cessation of retroviral drug therapy may simply be chance, Applicants respectfully submit that one of ordinary skill in the art would not have considered Ho et al. to have adequately taught a method of in permitting cessation of antiviral therapy on HIV-infected subjects, without virus rebound or with a delayed virus rebound or a decreased post-rebound viral load.

Accordingly, the Examiner's reliance on Ho et al. in establishing *prima facie* obviousness is misplaced on this basis alone.

One of Ordinary Skill in the Art Had No Motivation to Combine Ho et al. and Kent et al. or to Rely on Ho et al. Alone Because of the Absence of Correlation Between Immunogenicity and Virus Control During Treatment Interruption

Applicants maintain that those skilled in the art would not have been motivated to combine the referenced teachings by modifying the method of Ho et al. to additionally express IFN-γ as taught by Kent in order to enhance the HIV-specific immune response for at least the reasons set forth on pages 4-5 of the Response dated November 8, 2010. Specifically, Applicants maintain that Rosenwirth disclosed a subject exhibiting greater viral levels after stopping chemotherapy and a subject exhibiting reduced viral levels. Furthermore, Markowitz et al. discloses that all subjects examined experienced viral rebound when treatment was discontinued. Both Rosenwirth and Markowitz et al. evidence a lack of correlation between

immunogenicity and virus control during treatment interruption, which would have discouraged those skilled in the art from repeating such attempts.

While the Examiner has argued that even without the disclosure of Kent et al., those skilled in the art would know that IFN-γ can be combined with the vaccine taught by Ho et al., Applicants submit that the results of Ho et al. are simply inadequate and statistically insignificant for supporting such proposal, as discussed above. Those skilled in art would be doubtful with the results of Ho et al., rather than motivated to follow the teachings of Ho et al. and to make further modifications by including IFN-γ.

Those of Ordinary Skill in the Art Would Have Had No Reasonable Expectaion of Success in Modifying the Protocol of Ho et al. to Arrive at the Claimed Invention

Applicants maintain that, even if *arguendo* there was a motivation to combine Ho et al. and Kent et al., those skilled in the art would not have had a reasonable expectation of success in arriving at the claimed invention for at least the reasons set forth on pages 5-6 of the Response dated November 8, 2010. Applicants maintain that this field of art is generally complex and fairly unpredictable, as evidenced by failed attempts of others. Applicants respectfully submit that Markowitz et al. further confirms this position in disclosing that "the immune responses that were measured were extremely variable, and no clear correlate of initial virologic suppression could be established" (page 642, first full paragraph, last sentence).

In addition, Applicants maintain that one of ordinary skill in the art would still have had to modify the teachings of Ho et al. to arrive at the presently-claimed subject matter, namely the administration of a nucleic acid vector rather than a protein antigen. Because of the complexity of the art, the failure of others in the field, and the uncertainty in the art as to the reasons underlying the results disclosed, Applicants respectfully maintain that one of ordinary

skill in the art would have had no reasonable expectation of success for the modifications to the protocol of Ho et al. so as to arrive at the presently-claimed subject matter.

The Examiner Has Not Addressed Applicants' Disclosure of Unexpected Results

Applicants maintain that the subject application discloses unexpected results for at least the reasons set forth on pages 6-8 of the Response dated November 8, 2010. However, Applicants respectfully submit that the Examiner did not address Applicants' disclosure of unexpected results in the Advisory Action dated November 19, 2010. Applicants respectfully request that the Examiner address Applicants' previous assertions in the next communication issued in connection with the subject application.

In particular, Applicants have disclosed that administration of an avipox vector encoding an HIV antigen and interferon-γ to an HIV-infected subject in the absence of anti-retroviral drug treatment resulted a reduction or delay of viral rebound during interruption of anti-retroviral drug treatment, *in the absence* of a detectable immunological response to HIV (see, for example, the specification of the subject application at page 43, lines 22-25). The Examiner's attention is directed to the results of a clinical trial in humans described in the specification, showing that a pox virus vector encoding *gag* and/or *pol* and interferon-γ achieved a "10 fold reduction in average viral fold" was observed despite of "the lack of any demonstrable immune response in the early part of the trial" (page 43, lines 22-25).

Therefore, Applicants respectfully submit that they have disclosed, firstly, an avipox vector encoding an HIV antigen and interferon-γ suitable for administration to an HIV-infected subject in the absence of anti-retroviral drug treatment; and, secondly, such administration resulted in a reduction or delay of viral rebound during interruption of anti-retroviral drug

treatment, in the absence of a detectable immunological response to HIV. Applicants respectfully submit that these results were entirely unexpected

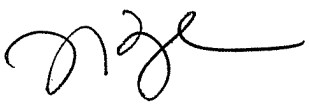
Summary

Because the teaching of Ho et al. is inadequate in the first instance, and because those of ordinary skill in the art would have had no motivation or reasonable expectation of success to further modify Ho et al. in order to arrive at the claimed invention, and because the results achieved in the present application are unexpected, the presently claimed invention is not obvious over Ho et al. in view of Kent et al. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

CONCLUSION

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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